UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,490	12/30/2003	Hiroyuki Tamaki	SAEG143.002AUS	8746

20995 7590 01/16/2007

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/16/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/748,490	TAMAKI ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II (claims 4-5, 9-11) in the reply filed on 11/16/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-3, 6-8 have been canceled in the amendment filed 11/16/2006. Original claims 4-5, 9-11 and new claim 12 (11/16/2006) are under consideration by the Examiner.

Claim rejections-35 USC § 112, first paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 4-5, 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treating inflammatory bowel disease by administering a protein belonging to the thioredoxin superfamily. The claims do not require that the administered polypeptide possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a method of administering a genus of polypeptides from the thioredoxin superfamily. To provide evidence of possession of a claimed

genus to be administered, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in claim 4, for example, is that a member of the thioredoxin family is to be administered. There is not even identification of any particular portion of the structure that must be conserved for the biological activity of the protein. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics and structure/function relationship, the specification does not provide adequate written description of the genus of polypeptides to be administered in the claimed method.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the ad that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description' inquiry, whatever is *now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of thioredoxin polypeptides to be administered, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only a method of administering to DSS-induced colitis in thioredoxin – transgenic (TRX-Tg) mice, a thioredoxin polypeptide comprising the amino acid sequence of SEQ ID NO:1, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

2b. Claims 4-5, 9-12, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

The specification delimits the instant method to alleviation of colitis symptoms in DSS-induced colitis in TRX-Tg mice. However, with respect to claims 4-5, 9-12, as recited, what is claimed in the instant invention encompasses a method of administering "all" members of the thioredoxin superfamily. The specification is non-enabling for such a method of administering these unlimited and unidentified number of substances, which are encompassed by the scope of the claims. Claim 1, for example, is a single means claim (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts have held that: A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. (A single

means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for "thioredoxin superfamily" have been recited in the claim and only a biological activity has been recited, the claim encompasses every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. The claimed invention encompasses a method of administering compositions not envisioned or described in the specification, and neither does the specification disclose how these compositions can be distinguished from each other. The specification only enables a method of administering recombinant human thioredoxin polypeptide to treat DSS-induced colitis in TRX-Tg mice, the polypeptide having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known proteins. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which members of the thioredoxin superfamily are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the methods taught in the specification unpredictable (see pages 14-17). Therefore, it would require undue experimentation to determine which substances having "thioredoxin" activity, would be encompassed by the method claims. The disclosure of using a recombinant human thioredoxin to treat DSS-induced colitis in a TRX-Tg mice model is clearly insufficient support under the first paragraph of 35 U.S.C. 112 for claims

which encompass a method of administering to patients, including humans, effective amounts of every and all members of the thioredoxin superfamily. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable compositions, may be innumerable, and the enabled embodiments amounts to none because thioredoxin was never administered to treat IBD. Therefore, there are substantial scientific reasons to doubt the enablement, as set forth above. Reasonable correlation must exist between the claims and enablement set forth. The specification does not describe administering any thioredoxin

polypeptide to patients. The specification only demonstrates that in DSS-treated TRX-Tg mice the colitis symptoms were alleviated.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to practice the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, i.e., methods of treatment, a certain amount of enablement beyond mere assertion must be required.

The method of the instant claims comprises the administration to humans a polypeptide that is a member of the thioredoxin superfamily to treat inflammatory bowel disease (IBD). The specification on page 16-17, discloses:

"As demonstrated by the Examples, (I) the investigation using TRX-Tg mice showed the importance of TRX in colitis inhibition, and (2) therapeutical administration of TRX alone can rectify pathological conditions of colitis. These facts suggest the effectiveness of TRX as a therapeutic agent for treating inflammatory bowel diseases such as ulcerative colitis and the

like."

Except for demonstrating the alleviation of the tissue damage which was rectified in DSS-treated TRX-Tg mice, the specification fails to demonstrate the effect of administering thioredoxin in any patients including humans. The instant specification does not adequately teach how to effectively treat IBD in other animals such as humans by administering thioredoxin.

Sido et al. (2005) disclose that thioredoxin expression was elevated in the intestinal mucosa in IBD in humans suggesting that TRX is involved in intestinal immune responses (see abstract, page 408; page 409, column 1, first full paragraph). While the instant specification discloses on page 15, lines 10-18, that in the wild-type DSS group inflammatory cell infiltration, crypt damage and sore and ulcer formation was observed, rectification of these symptoms was observed in the TRX-transgenic-DSS mice. However, the recombinant human TRX was never administered to these mice. There is insufficient guidance in the specification as filed, to allow one skilled in the art to practice the instant method without extensive and undue experimentation.

The CAFC decision (Genentech Inc. v. Novo Nordisk, 42 USPQ2d 1001, 1997) expressly states that:

"When there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

In the instant case, a method of treating IBD by administering thioredoxin has not been enabled by the instant specification. The instant situation is directly analogous to that which was addressed in In re Colianni, 195 U.S.P.Q. 150, C.A.F.C., which held that a "disclosure that calls for application of 'sufficient' ultrasonic energy to practice claimed method of fusing bones but does not disclose what 'sufficient' dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. § 112 first paragraph".

Thus, it would require undue experimentation on the part of the skilled artisan to use the claimed method for treatment of IBD as recited, in the absence of sufficient information to predict the results with an adequate degree of certainty. In view of this unpredictability in the treatment of IBD, there cannot be said to be any reasonable expectation of success at the in vivo application of a potential therapy, especially in view of the fact that the current specification as filed presents no working examples pertaining to a method of treatment of IBD by administering TRX in vivo. Therefore, a method of treatment of IBD by administering a member of the thioredoxin superfamily as recited in the claims has not been enabled by the specification.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-5, 9-12, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4, lines 3-4, is vague and indefinite because it recites "thioredoxin superfamily". The metes and bounds of this term are unclear. The specification recites on page 8, lines 6-11, that "Examples of polypeptides of the TRX family include those having the sequences: -Cys-Gly-Pro-Cys-, -Cys-Pro-Tyr-Cys-, -Cys-Pro-His-Cys-, or -Cys-Pro-Pro-Cys- in the active site. Among these, preferable are those having the sequence -Cys-Gly-Pro-Cys- in the active site.". However, these recitations are only examples of members of the thioredoxin superfamily.

Claim 9, lines 1-2, is vague and indefinite because it recites "wherein the thioredoxin superfamily is an isolated peptide having thioredoxin(TRX) activity". It is unclear how the thioredoxin superfamily can be a single peptide. Furthermore, the metes and bounds of the term "thioredoxin activity" are unclear. Which activity/activities of thioredoxin are encompassed by the term "thioredoxin activity"?

Claim 9 recites the limitation "peptide" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 4 recites "polypeptide".

Regarding claim 9, line 2, the phrase "including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 10, is vague and indefinite because it recites "the thioredoxin superfamily is in reduced form". This recitation is improper because the thioredoxin polypeptide is in reduced form.

Claim 11 is vague and indefinite because it recites "the method... which is in the form of solution or suspension....". This recitation is incorrect because the polypeptide is in solution or suspension.

Claims 5, 12, are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Conclusion

No claim is allowed.

Claims 4-5, 9-12, are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D., J.D.
Primary Examiner
Art Unit 1646
January 3, 2007